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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
PAK, YONG D

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 04/21/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/776,191	MADISON ET AL.	
	Examiner	Art Unit	
	Yong D. Pak	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *1-3, 5, 10-13, 19-20, 34-36, 40-46, 48-55, 108-109 113-116, 118-120 and 122-126* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5,11-13,19,20,34-36,40-42,113 and 114* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1-3,5,10-13,19,20,34-36,40-46,48-55,108,109,113-116,118-120 and 122-126.

DETAILED ACTION

This application is a CIP of 09/657,986, now issued as U.S. Patent No. 6,797,504.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January 30, 2006, amending claims 1, 5, 12-13, and 113-114 and canceling claims 6-7, 9-10, 14, 16, 18 and 137, has been entered.

Claims 1-3, 5, 10-13, 19-20, 34-36, 40-46, 48-55, 108-109 113-116, 118-120 and 122-126 are pending. Claims 1-3, 5, 10-13, 19-20, 34-36, 40-46, 48-55, 108-109 113-116, 118-120 and 122-126 are withdrawn. Claims 1-3, 5, 11-13, 19-20, 34-36, 40-42 and 113-114 are under consideration.

Priority

Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. However, the provisional applications upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for claims 11-13 and 34 of this application.

Provisional applications 60/179,982, 60/183,542, 60/213,124, 60/220,970 and 60/234,840 fail to provide adequate support for polypeptides comprising the serine protease domain of MTSP1. Provisional applications 60/179,982 and 60/183,542 describe polypeptides related MTSP3 and provisional application 60/213,124, 60/220,970 and 60/234,840 describe polypeptides related to MTSP4.

Therefore, the effective filing date for purpose of prior art is the filing date of 09/657,986, which is 9/8/2000.

Response to Arguments

Applicant's amendment and arguments filed on January 30, 2006, have been fully considered and are deemed to be persuasive to overcome the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Objections

Claims 11-13 and 34 are objected for being drawn to non-elected subject matter. In response to the previous Office Action, applicants have traversed the above rejection. Applicants argue that claims 11-13 and 34 are directed to elected subject matter. Even though claims are drawn to MTSP1, the elected subject matter, the claims are also drawn to non-elected subject matter, i.e. MTSP3 (SEQ ID NO:4), MTSP4 (SEQ DI NO:6), MTSP6 (SEQ DI NO:12), corin, enteropeptidase, human airway trypsin-like protease , TMPRSS2, TMPRSS4. Hence the objection is maintained.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3, 5, 11-12, 13 and claims 19-20, 34-36, 40-42 and 113-114 depending therefrom rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-3, 5, 11-12, 13 recite the phrase "substantially purified single-chain polypeptide". The metes and bounds of the phrase in the context of the above claims are not clear to the Examiner. It is not clear to the Examiner what is considered as "substantially purified" by the applicants. A perusal of the specification did not provide a clear definition for the above phrase. Without a clear definition, those skilled in the art would be unable to conclude if a polypeptide is a "substantially purified" polypeptide without knowing the metes and bounds of the phrase. Examiner requests clarification of the above phrase.

Claim 1 and claims 2-3, 5, 11-13, 19-20, 34-36, 40-42 and 113-114 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the phrase "the MTSP protease domain or catalytically active fragment thereof is the only portion of the single-chain polypeptide from the MTSP".

The metes and bounds of the phrase in the context of the claim is not clear. It is not clear to the Examiner as to how one skilled in the art would identify a given amino acid sequence as being "from MTSP" or not being "from MTSP". Examiner has interpreted the claims broadly to mean that a "single-chain polypeptide comprising a MTSP protease domain or catalytically active fragment thereof is the only portion of the single-chain polypeptide from the MTSP" is a "single-chain polypeptide comprising a fragment consisting of a protease domain or a catalytically active fragment thereof". Examiner requests clarification of the above phrase.

Claims 12-13 and claims 113-114 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 12-13 recite the phrase "protease domain has a sequence of amino acid residues set forth as amino acids 615-855 of SEQ ID NO:2" or "protease domain whose sequence of amino acid residues is set forth as amino acid residues 615-855 of SEQ ID NO:2". The metes and bounds of the phrase in the context of the claims are not clear. It is not clear to the Examiner if the recited amino acid sequence has the amino acid sequence of SEQ ID NO:2 or is a representative member of a genus. Examiner suggests amending the phrase as "protease domain comprises amino acids 615-855 of SEQ ID NO:2" to clearly indicate that the protease domain has the amino acids 615-855 of SEQ ID NO:2.

Claim 19-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 19-20 recite the phrase "free Cys". The metes and bounds of the phrase in the context of the above claims are not clear to the Examiner. It is not clear to the Examiner what is considered as "free Cys" by the applicants. A perusal of the specification did not provide a clear definition for the above phrase. Without a clear definition, those skilled in the art would be unable to conclude if Cys is "free". Examiner requests clarification of the above phrase.

Claim 19 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 19 recites the phrase "exhibits proteolytic activity". The metes and bounds of the phrase in the context of the above claim are not clear to the Examiner. It is not clear to the Examiner either from the specification or from the claims as to what applicants mean by the above phrase. Examiner requests clarification of the above phrase.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 5, 9, 11, 19-20, 34-36, 40-42 and 113-114 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-3, 5, 9, 19-20, 35-36, 40-42 and 113-114 are drawn to a polypeptide comprising a protease or catalytically active portion of type-II membrane-type serine protease (MTSP) from any source. Claims 11 and 34 limit the MTSP polypeptide to a MTSP1 polypeptide from any source. Therefore, these claims are drawn to a genus of polypeptides having any structure. The specification only teaches four species, amino acids 615-855 of SEQ ID NO:2, amino acids of 205-437 of SEQ ID NO:4, amino acids of SEQ ID NO:6 and amino acids 217-443 of SEQ ID NO:11. These species are not enough to describe the whole genus and there is no evidence on the record of the relationship between the structure of the above catalytically active protease domains of SEQ ID NOs: 2, 4, 6 and 11 and the structure of the serine protease domain of any or all MTSP polypeptides or MTSP1 polypeptides. Further, the specification does not describe the structure of a catalytically active portion of any or all MTSP polypeptide. Therefore, the specification fails to describe a representative species of the genus of polypeptides comprising of a serine protease domain or a catalytically active portion of a MTSP polypeptide.

Given this lack of description of the representative species encompassed by the genus of the claims, the specification fails to sufficiently describe the claimed invention

in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the inventions of claims 1-3, 5, 9, 11, 19-20, 34-36, 40-42 and 113-114.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

In response to the previous Office Action, applicants have traversed the above rejection.

Applicants argue that the claims meet the written description guideline since the specification teaches common elements of MTSP and protease domains of MTSPs, thereby providing structural and functional characteristics of the various species. Applicants also argue that the specification explicitly provides several catalytically active portions of MTSP, SEQ ID NO:2, 4, 6 and 11 (MTSP1, MTSP3, MTSP4 and MTSP 6), along with how to make other catalytically active fragments of MTSP, and therefore, the specification provides "relevant, identifying characteristics" of a representative number of species of the claimed genus. Examiner respectfully disagrees. The claims are drawn to polypeptides comprising any protease domains or any or all catalytically active fragments of said protease domains of any or all MTSP or any or all MTSP1, including any or all recombinants, variants and mutants of said MTSP or MTSP1. The claims are drawn to polypeptides having any structure and therefore, the claims are drawn to a genus encompassing species having substantial variation and fails to describe a representative number of species. As discussed in the written description guidelines,

the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. A representative number of species means that the species which are adequately described are representative of the entire genus. **Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.** Satisfactory disclosure of a representative number depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. For inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus. In the instant case the claimed genera of the claims are drawn to species which are widely variant in structure. The genus of the claims are structurally diverse as it encompasses any catalytically active protease domains of any or all MTSP or MTSP1, excepting having serine protease activity. As such, neither the description of solely structural features present in all members of the genus is sufficient to be representative of the attributes and features of the entire genus.

Hence the rejection is maintained.

Claims 1-3, 5, 9, 19-20, 34-36, 40-42 and 113-114 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polypeptide comprising amino acids 615-855 of SEQ ID NO:2, does not reasonably provide enablement for a polypeptide comprising any protease domain of any type II membrane type serine protease (MTSP) or MTSP1 or a catalytically active portion thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Claims 1-3, 5, 9, 19-20, 35-36, 40-42 and 113-114 are drawn to a polypeptide comprising a protease or catalytically active portion of type-II membrane-type serine protease (MTSP) from any source. Claims 11 and 34 limit the MTSP polypeptide to a MTSP1 polypeptide from any source. Therefore, these claims are drawn to polypeptides having undefined structure.

The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polypeptides comprising a

protease or catalytically active domain broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the polypeptide comprising amino acids 615-855 of SEQ ID NO:2, or the amino acids of SEQ ID NO:50.

It would require undue experimentation of the skilled artisan to make and use the claimed polypeptides. The specification is limited to teaching the use of polypeptide comprising amino acids 615-855 of SEQ ID NO:2 or the amino acids of SEQ ID NO:50 but provides no guidance with regard to the making of variants and mutants or with regard to other uses. In view of the great breadth of the claim, amount of experimentation required to make the claimed polypeptides, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure, the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polypeptides encompassed by the claims.

While enzyme isolation techniques, recombinant and mutagenesis techniques are known, and it is routine in the art to screen for multiple substitutions or multiple modifications as encompassed by the instant claims, the specific amino acid positions

within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and variants of a protease or catalytically active domain or modifications of amino acids 615-855 of SEQ ID NO:2 because the specification does not establish: (A) regions of the protein structure which may be modified without affecting MTSP/serine protease activity; (B) the general tolerance of MTSP to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including protease or catalytically active domains of MTSP with an enormous number of amino acid modifications of the MTSP polypeptides and of amino acids 615-855 of SEQ ID NO:2. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of the serine protease domain or the catalytically active domain of MTSP having the desired biological

characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

In response to the previous Office Action, applicants have traversed the above rejection.

Applicants argue that the level of skill in this art is high and the specification teaches structural and functional features sufficient to enable one of skill in the art to make sue the single chain polypeptides comprising catalytically active portion of an MTSP protease domain, by providing structure of MTSP polypeptides and their protease domains, as well as their conserved structures. Examiner respectfully disagrees. The scope of the claims, which are drawn to polypeptides comprising any protease domains or any or all catalytically active fragments of said protease domains of any or all MTSP or any or all MTSP1, including any or all recombinants, variants and mutants of said MTSP or MTSP1, is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polypeptides comprising a protease or catalytically active domain broadly encompassed by the claims. Even though the structure of some MTSP are known, the claims are drawn to any or all catalytically active fragments of any or all protease domains of any or all MTSP or MTSP1. As discussed above, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a specific knowledge of and guidance with regard to which specific amino acids in the protein's sequence, can be modified such that the modified polypeptide continues to have said

claimed activity. It is this specific guidance that applicants do not provide. While the art may teach in general the structure of MTSP conserved amino acid sequences, protease domains, X-ray crystal structure and etc, such teachings will not reduce the burden of undue experimentation on those of ordinary skill in the art.

Applicants argue that the specification discloses working examples, thus a person skilled in the art has sufficient guide in making the claimed polypeptides. Examiner respectfully disagrees. Even though the structure of some MTSP are taught, the claims are not only drawn to polypeptides comprising catalytically active fragments of only MTSP1, MTSP3, MTSP4 and MTSP6, but to any or all mutants, variants and recombinants of any MTSP. Without specific guidance, those skilled in the art will be subjected to undue experimentation of making and testing each of the enormously large number of mutants that results from such experimentation. While the art may teach in general the structure of MTSP, conserved amino acid sequences, and etc, such teachings will not reduce the burden of undue experimentation on those of ordinary skill in the art.

Hence the rejection is maintained.

Applicants argue that it would be unfair, unduly limiting and contrary to the public policy upon which the patent laws are based to require applicant to limit the instant claims to only one exemplified protease domain. This argument is moot since patentability is based on statutes under 35 USC 101, 112, 102 and/or 103.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-3, 5, 11-13, 19-20, 34-36, 40-42 and 113-114 are rejected under 35 U.S.C. 102(b) as being anticipated by Takeuchi et al. (see rejection of the phrase "MTSP protease domain or catalytically active fragment there is the only portion of the single-chain polypeptide from the MTSP" under 35 USC 112, 2nd paragraph above)

Claims 1-3, 5, 11-13, 19-20 and 34 are drawn to a polypeptide comprising fragment consisting of a serine protease domain of MTSP having the characteristics recited in the claims. Claims 35-36 are drawn to a conjugate comprising a polypeptide comprising a serine protease domain of MTSP and a targeting agent. Claims 40 –42 and 113-114 are drawn to a solid support comprising a polypeptide comprising a serine protease domain of MTSP.

Takeuchi et al. (Reference IJ : PTO-1449) teaches a polypeptide comprising a fragment consisting of a serine protease domain that is 100% identical to amino acids 615-855 of SEQ ID NO:2 of the instant invention (page 11060, 2nd full paragraph). Takeuchi et al. discloses a purified activated protease domain, comprising amino acids

615-855 of SEQ ID NO:2, confirmed by an N-terminal sequence of the purified, activated protease domain yielding the expected VVGGT sequence (Figure 3 and right column on page 11057). The MTSP of Takeuchi et al. is not expressed on normal endothelia cells (page 11054, last paragraph and page 11055, 2nd full paragraph), is of human origin (Figure 1), consists essentially of the protease domain having catalytic activity (page 11060, 2nd full paragraph), and is expressed in tumor cells (page 11055, top paragraph).

Takeuchi et al. teaches a catalytically active polypeptide comprising the serine protease domain linked to a His-tag (page 11055, 3rd full paragraph, page 11057, 4th full paragraph). Takeuchi et al. also teaches a solid support comprising said polypeptide (page 11057, 4th full paragraph and Figure 5). Therefore, the teaching of Takeuchi et al. anticipates claims 1-3, 5, 11-13, 19-20, 34-36, 40-42 and 113-114 are.

Examiner notes that the contents of the reference were made public at the National Academy of Sciences colloquium held February 20-21, 1999 (see top of reference).

In response to the previous Office Action, applicants have traversed the above rejections.

Applicants argue that Takeuchi et al. does not anticipate the instant claims because it fails to disclose any polypeptides that incorporate all the features of claim 1, a single chain polypeptide having an MTSP portion, wherein the MTSP portion is a protease domain or a smaller fragment and wherein the MTSP portion has serine protease activity.

Applicants argue that the MT-SP1 of Takeuchi et al. is a full-length protein that includes additional MTSP regions other than a protease domain, and therefore, said MTSP1 of Takeuchi et al. is not a polypeptide where the only MTSP portion of the polypeptide is a protease domain or a smaller catalytically active portion of the protease domain. Examiner respectfully disagrees. First, the claim recites "a polypeptide comprising a MTSP portion" and the claim does not recite the limitation that the polypeptide only consist of MTSP portion. Therefore, a full-length MT-SP1 of Takeuchi et al. anticipates the instant claims. Second, in addition to the full-length MT-SP1, Takeuchi et al. also discloses a purified activated protease domain, comprising amino acids 615-855 of SEQ ID NO:2, confirmed by an N-terminal sequence of the purified, activated protease domain yielding the expected VVGGT sequence (Figure 3 and right column on page 11057). Even applicants state that Takedeuchi et al. discloses "that its protease domain has an amino acid sequence containing amino acids 615-855 (Remarks page 36) and that "Takeuchi et al. discloses that its polypeptide includes the pro-domain and that the pro-domain is cleaved during auto-activation, resulting in a protease domain" (page 37). Therefore, said purified, activated protease domain anticipates the instant claims.

Applicants also argue that the reference of Takeuchi et al. does not anticipate the instant claims because the "purified protease domain" of Takeuchi et al. includes the His-tag sequence and that the polypeptide construct disclosed by Takeuchi et al. includes a sequence of 19 amino acids of a portion of the pro-domain and that his pro-domain is disulfide bonded to the protease domain. Examiner respectfully disagrees.

Takeuchi et al. also discloses a purified activated protease domain, comprising amino acids 615-855 of SEQ ID NO:2, confirmed by an N-terminal sequence of the purified, activated protease domain yielding the expected VVGGT sequence (Figure 3 and right column on page 11057 and Figure 6). Further, applicants state that "Takeuchi et al. discloses that its polypeptide includes the pro-domain and that the pro-domain is cleaved during auto-activation, resulting in a protease domain" (page 37).

Applicants also argue that the activated protein derived from the expressed His-tag amino acids 596-855 of MT-SP1 of Takeuchi et al. is not a single chain polypeptide because the protease domain is disulfide bonded to a pro-doiamin resulting in a two chain form. Examiner respectfully disagrees. Takeuchi et al. discloses that the pro-domain is disulfide bonded to a protease domain of the full length protein. Contrary to applicants argument, Takeuchi et al. does not teach that the pro-domain is disulfide bonded to an activated protease domain. Further, a single chain polypeptide is one sequence of amino acids beginning with a carboxyl end and terminating with an amino end, wherein the amino acids are connected via peptide bonds. Therefore, even the full length MT-SP1 of Takeuchi et al. having disulfide bonds can be construed as a single chain polypeptide.

In conclusion, Takeuchi et al. discloses a purified activated protease domain, comprising amino acids 615-855 of SEQ ID NO:2, confirmed by an N-terminal sequence of the purified, activated protease domain yielding the expected VVGGT sequence (Figure 3 and right column on page 11057 and Figure 6). Further, applicants state that

"Takeuchi et al. discloses that its polypeptide includes the pro-domain and that the pro-domain is cleaved during auto-activation, resulting in a protease domain" (page 37).

Hence the rejections are maintained.

Claim Rejections - 35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The following is a quotation of 35 U.S.C. 103(a), which forms the basis for all obviousness rejections, set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 5, 10-13 and 34 rejected under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over O'Brien et al.

Claims 1-3, 5, 10-13 and 34 are drawn to a polypeptide comprising a serine protease domain of MTSP.

O'Brien et al. (U.S. Patent No. 5,972,616 – reference P- PTO 1449) teaches a polypeptide having 100% identity to the full length MTSP1 of SEQ ID NO:2 of the instant invention (SEQ ID NO:2, columns 19-24). The properties recited in claims 2-3 are

inherent properties of MTSP1 taught by O'Brien et al. since the polypeptide of O'Brien et al. and the instant invention have identical structure and therefore identical properties.

O'Brien et al. teaches a serine protease domain having proteolytic activity that is 100% identical to amino acids 615-855 of SEQ ID NO:2 (Figure 2, Figure 10 and SEQ ID NO:14). Although the protease domain of O'Brien et al. identified by SEQ ID NO:14 has not been purified, the protease domain in the reference and the polypeptide claimed by the applicants are one and the same. Therefore, the protease domain anticipates the instant invention.

Since the Office does not have facilities for examining and comparing applicant's polypeptide with the polypeptide of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the polypeptide of the prior art does not possess the same material structure and functional characteristics of the claimed polypeptide). See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Figzgerald* et al., 205 USPQ 594.

Alternatively, O'Brien et al. teaches a method of expressing polypeptides via a vector in host cells. O'Brien et al. also teaches that the protease domain could be released the used as a diagnostic which has the potential for a target for therapeutic intervention (Column 15, lines 35-38). Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to express the protease domain of SQ ID NO:14 and purify the polypeptide. The motivation of making such a polypeptides is to use it as a diagnostic which has the potential for a target for

therapeutic intervention. One of ordinary skill in the art would have had a reasonable expectation of success since expression of a heterologous polypeptide is routine in the art and O'Brien et al. teaches how to express heterologous polypeptides.

In response to the previous Office Action, applicants have traversed the above rejections.

Applicants argue that O'Brien et al. does not anticipate any of the instant claims because the claims are not directed to a full-length MTSP polypeptide. Examiner respectfully disagrees. The claim recites "a polypeptide comprising a MTSP portion" and the claim does not recite the limitation that the polypeptide only consist of MTSP portion. Therefore, the full-length MT-SP1 of O'Brien et al. anticipates the instant claims.

Applicants also argue that one of skill in the art would recognize the disclosure of the polypeptide of O'Brien as not disclosing a single chain polypeptide. Examiner respectfully disagrees. A single chain polypeptide is one sequence of amino acids beginning with a carboxyl end and terminating with an amino end, wherein the amino acids are connected via peptide bonds. Therefore, the full length MT-SP1 of O'Brien et al. can be construed as a single chain polypeptide.

Applicants argue that one of skill in the art would understand MTSP serine proteases to be active only as two chain polypeptides by citing Lu et al. (1999) *J. Biol. Chem.* 272:31293-300 and would not view O'Brien et al. as disclosing a single chain polypeptide. Examiner respectfully disagrees. The bibliographi information Lu et al. (1999) *J. Biol. Chem.* 272:31293-300 could not be located through *J. Biol. Chem.*

Applicants are urged to supply the reference or the correct bibolographic information. Nevertheless, applicants state that "as expressed, the MTSP polypeptide is an inactive single-chain zymogen" (Remarks page 42). Therefore, according to applicants, the full length MT-SP1 of O'Brien et al. is a single chain polypeptide and therefore, anticipates the claimed invention.

Hence the rejection is maintained.

Applicants also argue that O'Brien et al. provides no teaching or suggestion of smaller fragments having serine protease activity because it does not teach how to make a single chain polypeptide that has serine protease activity. Examiner respectfully disagrees. O'Brien et al. teaches a method of expressing polypeptides via a vector in host cells. It is well within the skill available in the art to purify the protease domain since O'Brien et al. identifies the protease domain. Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to express the protease domain of SQ ID NO:14 and purify the polypeptide. The motivation of making such a polypeptides is to use it as a diagnostic which has the potential for a target for therapeutic intervention. One of ordinary skill in the art would have had a reasonable expectation of success since expression of a heterologous polypeptide is routine in the art and O'Brien et al. teaches how to express heterologous polypeptides.

Applicants again argue that at the time of filing the instant application, one of skill in the art would not have had a reasonable expectation of success to express the

protease domain because art evidences that a single-chained polypeptide would not have been expected to have protease activity. Examiner respectfully disagrees. The claims are drawn to a polypeptide comprising a fragment consisting of a protease domain of SEQ ID NO:2. Therefore, said polypeptide being a single-chained polypeptide is an inherence property of said polypeptide since two polypeptides having identical structure will have identical function and physical and chemical properties. Hence the rejections are maintained.

Claims 35-36, 40-42 and 113-114 are rejected under 35 U.S.C. 103(a) as being unpatentable over O'Brien et al.

Claims 35-36 are drawn to a conjugate comprising a polypeptide comprising a serine protease domain of MTSP and a targeting agent. Claims 40-42 and 113-114 are drawn to a solid support comprising a polypeptide comprising a serine protease domain of MTSP.

O'Brien et al. (U.S. Patent No. 5,972,616 – reference P- PTO 1449) teaches a polypeptide having 100% identity to the full length MTSP1 of SEQ ID NO:2 of the instant invention, as discussed above. O'Brien et al. also teaches that the protease domain could be released the used as a diagnostic which has the potential for a target for therapeutic intervention (Column 15, lines 35-38).

O'Brien et al. also teaches method of making fragments of SEQ ID NO:2 (Column 9, lines 22-55). O'Brien et al. teaches said fragments linked to another polypeptide (Column 9, lines 54-55) and conjugated to bridging molecules (Column 6,

lines 27-39) for detecting the polypeptide. Assays using polypeptides linked to the molecules taught by O'Brien et al. utilize solid supports.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to make a polypeptide comprising of the serine protease domain of SEQ ID NO:2 taught by O'Brien et al. and to make conjugates and solid support comprising of a polypeptide comprised of the serine protease domain of SEQ ID NO:2. The motivation of making such a polypeptides is to use it as a diagnostic which has the potential for a target for therapeutic intervention. The motivation of making conjugates and solid supports comprising of said polypeptide is to use the conjugate and solid support in a variety of diagnostic assays. One of ordinary skill in the art would have had a reasonable expectation of success making fragments of a polypeptide is routine in the art and O'Brien et al. teaches how to make fragments of SEQ ID NO:2. One of ordinary skill in the art would have had a reasonable expectation of success in diagnostic assays using conjugates and solid supports comprising a polypeptide is very well known, as taught by O'Brien et al.

Therefore, the above references render claims 35-36 and 40-42 *prima facie* obvious to one of ordinary skill in the art.

In response to the previous Office Action, applicants have traversed the above rejections. Applicants argue that the teachings of O'Brien et al. does not result in the instantly claimed compositions because O'Brien et al. does not teach or suggest a single chain polypeptide that includes a MTSP protease domain where the polypeptide

does not include any additional MTSP portions and the polypeptide has serine protease activity. O'Brien et al. does teach or suggest a single chain polypeptide comprising a MTSP portion, wherein the MTSP portion is a protease domain and wherein the MTSP portion has serine protease activity and wherein the MTSP portion is the only portion of the polypeptide because O'Brien et al. identifies the serine protease domain and one having ordinary skill in the art at the time the invention was filed would have been motivated to purify the serine protease domain of O'Brien et al. as discussed above.

Hence the rejection is maintained.

Claims 19-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over O'Brien et al. and Estell et al. in view of Takeuchi et al.

Claims 19-20 are drawn to a polypeptide comprising the serine protease domain of a MTSP wherein free Cys residues are substituted with Ser residues.

O'Brien et al. teaches a serine protease domain of a MTSP polypeptide, as discussed above.

The reference of O'Brien et al. does not teach a serine protease domain of a MTPSP polypeptides wherein free Cys residues have been replaced with Ser residues.

It is well known in the art that proteins form disulfide bonds via the SH groups of Cys residues. Upon making a polypeptide comprising a serine protease domain, a Cys residue which normally forms disulfide bonds in the full length polypeptide may be left free. For example, Takeuchi et al. (Reference IJ : PTO-1449) teaches that Cysteine at

position 731 of SEQ ID NO:2 normally forms a disulfide bond with a Cys residue in the pro-protease domain (see page 11060, top left paragraph and Figures 1 and 2).

Cys residues are sensitive to oxidation due to their SH side group. Estell et al. (U.S. Patent No. 5,346,823) teaches that Cys residues replaced with Ser residues to decrease a polypeptide's susceptibility to oxidation (Abstract and Column 10, lines 34-38). Ser residues have similar side chains as Cys residues and substitution of a Cys residue with a Ser residue is a conservative substitution.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to replace free Cys residues in the protease domain taught by O'Brien et al. with a Ser residue. One of ordinary skill in the art would be motivated to make such a change in order to enhance stability of the polypeptide. One of ordinary skill in the art would have had a reasonable expectation of success since Estell et al. teaches successful decrease of a protein's susceptibility to oxidation by substituting residues sensitive to oxidation with conservative substitutions.

Therefore, the above references render claims 1 and 16, 18-20, 34 and 137 *prima facie* obvious to one of ordinary skill in the art.

In response to the previous Office Action, applicants have traversed the above rejections. Applicants argue that the combination of the teachings of O'Brien et al. with the teachings of Estell et al., and Takeuchi et al. does not result in the instantly claimed methods because O'Brien et al. does not teach or suggest a single chain polypeptide that includes a MTSP protease domain where the polypeptide does not include any

additional MTSP portions and the polypeptide has serine protease activity and that neither Takeuchi et al. nor Estell et al. remedy the defects of O'Brien et al. First, the claims are product claims and not method claims. Second, O'Brien et al. does teach or suggest a single chain polypeptide comprising a MTSP portion, wherein the MTSP portion is a protease domain and wherein the MTSP portion has serine protease activity and wherein the MTSP portion is the only portion of the polypeptide because O'Brien et al. identifies the serine protease domain and one having ordinary skill in the art at the time the invention was filed would have been motivated to purify the serine protease domain of O'Brien et al. as discussed above.

Applicants argue that Takeuchi et al. teaches that every cysteine residue of the protein is disulfide bonded and therefore Takeuchi eta l. does not teach or suggest an MTSP protease domain having a free Cys residue. Examiner respectfully disagrees. Figure 4 applicants are referring to illustrate disulfide bonds of cysteine residues of the full length MTSP, for example, the Cys at position 830 is disulfide bonded to Cys at position 191.

Hence the rejections are maintained.

None of the claims are in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong Pak whose telephone number is 571-272-0935. The examiner can normally be reached 6:30 A.M. to 5:00 P.M. Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned are 571-273-8300 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

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